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ORIGINAL ARTICLE

The relationship between body-mass index, physical activity, and pathologic and clinical outcomes after radical prostatectomy for prostate cancer

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Abstract

Purpose We evaluated whether an increased body-mass index (BMI) and decreased physical activity increase the risk of locally advanced or high-risk prostate cancer (PCa) at radical prostatectomy (RP), and treatment failure after surgery.

Methods Data were collected from the PROCURE Biobank, a prospective cohort of patients with localized PCa undergoing RP in four academic centers in Québec between 2006 and 2013. Treatment failure was defined as biochemical recurrence and/or initiation of secondary, non-adjuvant therapy, and analyzed using the Kaplan–Meier method, log-rank tests, and Cox proportional-hazards models. Uni- and multivariate (ordered) logistic regression was used for time-independent variables.

Results 1813 patients were included. Median follow-up time was 69 months. Patients who reported a lower BMI were generally older, of Asian descent, and physically more active ($p < 0.05$). Younger, black, and overweight/obese patients reported less physical activity ($p < 0.05$). In multivariate analyses, a higher BMI increased the risk for locally advanced, high-risk PCa (defined as a pT3, N1 and/or Gleason 8–10 tumor; odds ratio 1.33, $p < 0.001$), but increased physical activity did not predict high-risk disease (odds ratio 0.84, $p = 0.39$). Patients with a higher BMI also had a larger prostate at surgery (odds ratio 1.13, $p = 0.03$). BMI and physical activity were not associated with positive surgical margins or time to treatment failure ($p > 0.05$).

Conclusions BMI was an independent predictor for locally advanced, high-risk disease in this cohort of PCa patients undergoing RP, but was unrelated to treatment failure. Physical activity was not related to locally advanced, high-risk PCa or treatment failure.

Keywords Prostatic neoplasms · Body-mass index · Exercise · Prostatectomy · Treatment failure

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Introduction

Prostate cancer (PCa) has the highest incidence rate and second highest mortality rate of cancers in men in North America [1]. Since PCa incidence increases with age and most tumors have a relatively indolent growth, there is a need to identify men that are at increased risk for advanced, aggressive PCa to target men that may benefit more from screening and treatment [2]. Currently, the Gleason score is the most widely used biomarker to identify aggressive PCa, together with other characteristics such as serum prostate-specific antigen (PSA) levels and TNM-staging [3]. However, additional risk factors for locally advanced and aggressive PCa are needed [4].

Obese men, as measured by the body-mass index (BMI), may have more advanced PCa at diagnosis and more aggressive disease [5]. These associations may occur due to detection biases (PSA hemodilution and larger prostates) and/or obesity-related biological mechanisms (elevated circulating growth factors, elevated estrogen levels, and/or chronic subclinical inflammation). However, published studies are inconclusive: meta-analyses conclude that BMI increases the biochemical recurrence rate after treatment, but also find publication bias in favor of a positive association [6, 7]. Indeed, in the meta-analysis that analyzed patients who had radical prostatectomy as a primary therapy, the study that was assigned the most weight did not find an association between BMI and biochemical recurrence [6]. More recent studies did not find an association either [8, 9]. Hence, the association between BMI and advanced/aggressive PCa remains disputed.

Physical activity may also be a risk factor in the etiology of PCa, but has been studied less well than BMI [10]. Increased physical activity has been suggested to decrease PCa mortality [11]. Various mechanisms have been hypothesized to explain the potential association between physical activity and PCa, such as reduced oxidative stress and reduced prostate inflammation in physically active men [12]. However, the literature remains inconclusive and also prone to publication bias [13, 14].

If BMI and/or physical activity are risk factors for advanced and/or aggressive PCa, this finding could impact prevention, screening, and treatment of PCa, particularly since obesity has become of epidemic proportions and a sedentary lifestyle increasingly prevalent. Therefore, we used data from a large prospective cohort study in Québec province (Canada) to study the association between BMI, physical activity, and locally advanced and/or recurrent disease in surgically treated PCa patients.

Patients and methods

Study participants

We retrieved data from PROCURE, a large, prospective cohort study and biobanking project. PROCURE includes 1971 patients with localized PCa who underwent radical prostatectomy between 2006 and 2013 at one of the four Québec University Health Centers: McGill University Health Centre, Centre Hospitalier de l'Université (CHU) de Montréal, CHU de Sherbrooke, and CHU de Québec. Prior to surgery, patients completed a detailed socio-demographic and lifestyle questionnaire. PROCURE patients were excluded from our analyses if they had not returned their questionnaire, if follow-up was unavailable, or if no PCa was found in the surgery specimen (Fig. 1). To be included in the BMI and physical activity analyses, patients needed to have adequately answered the questions related to these topics. We also excluded patients who had a BMI below 18.5 ($n = 9$) for the BMI analyses.

Study ethics

Patients decided voluntarily to participate in the PROCURE Biobank. Informed consent was obtained from all individual participants included in the study. All local, national, and international laws regarding research with human data and materials were followed, including the Declaration of Helsinki. Permission was obtained from local medical ethics committees before the study was initiated, and is annually renewed (McGill University Institutional Review Board study A01-M04-06A, latest renewal January 16th, 2018).

Data collection and statistical analyses

Primary exposures were BMI, and average weekly physical activity in the 12 months prior to surgery. BMI was calculated by dividing the self-reported weight of the patient in kilograms by the squared height in meters. In line with the definition used by the Centers for Disease Control and Prevention (CDC), BMI was divided into normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obesity (BMI 30.0 or higher); obesity was divided into three classes: BMI 30.0–34.9, 35.0–39.9, or 40.0 or higher [15]. For physical activity, patients self-reported the average number of hours of physical activity per week in the year prior to radical prostatectomy, and entered the level of activity (light household work to playing sports). In the questionnaire, physical activity had been grouped into low (< 1 h/week), medium (1–4 h/week), or high (> 4 h/week).

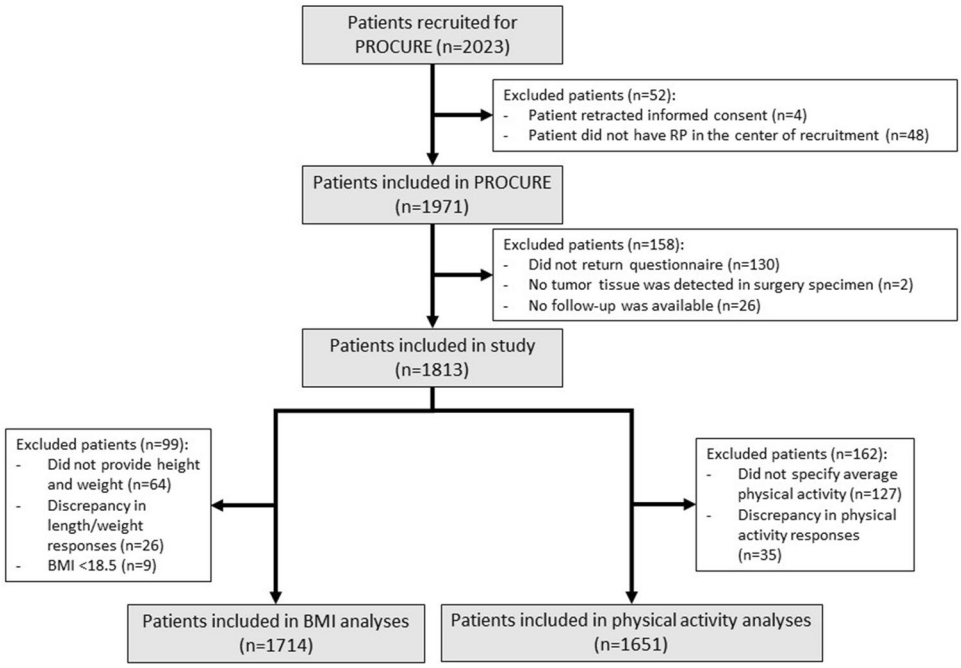

Fig. 1 Flow chart for patient inclusion. *BMI* body-mass index

Race was collected per FDA guidelines [16]. Prostate weight refers to its wet weight in grams, as determined before fixation and without the weight of the seminal vesicles. Histologic evaluation of prostatectomy specimens was conducted by genitourinary pathologists using a standardized protocol. Pathologic T-staging was divided into pT2, pT3a, and pT3b tumors. For the Gleason score, we used the 5-tier grading system recommended by the International Society of Urological Pathology [ISUP Grade Group (GG) 1: Gleason 6, GG2: Gleason 3 + 4, GG3: Gleason 4 + 3, GG4: Gleason 8, GG5: Gleason 9–10] [3]. Patients were considered to have high-risk PCa when having a pT3, pN1, and/or GG4/5 PCa. The CAPRA-S score was calculated according to Cooperberg et al. [17].

Treatment failure was considered two subsequent, rising PSA measurements above 0.2 ng/ml, or if salvage treatment was initiated (radiotherapy, androgen ablation), while the PSA was detectable but below 0.2 ng/ml. Patients with adjuvant therapy ($n = 17$) were censored at the start date of adjuvant therapy.

To compare baseline characteristics between patients grouped by BMI or physical activity, we categorized baseline characteristics, as described in Tables 1 and 2, and used Chi^2 tests to evaluate differences. Follow-up time was calculated by subtracting the date of last visit or last PSA measurement (whichever came last) by the date of radical prostatectomy for each patient. Uni- and multivariate (ordinal) logistic regression models were used to evaluate the association between BMI, physical activity, and surgery outcome parameters. For time-dependent variables, failure analyses were conducting using the Kaplan–Meier method and p values calculated with the log-rank test; hazard ratios were calculated using the Cox proportional-hazards model [18]. Stata version 15.1 was used for analyses.

Results

Of the 1971 patients included in PROCURE, 1714 were included in the BMI analyses and 1651 in physical activity analyses (Fig. 1). Median follow-up time was 69 months (interquartile range 54–87 months). Baseline characteristics are summarized in Tables 1 and 2. Since only 9 patients had a BMI of 40 or higher, we pooled class 2 and 3 obesity patients for analyses. Most patients were overweight (51.2%), and 19.2% of patients were obese (Table 1). BMI was inversely associated with age ($p = 0.02$), Asian descent ($p = 0.003$), and average weekly physical activity in the past year ($p < 0.001$). Patients most frequently exercised 1–4 h per week (49.5%, Table 2). Lower physical activity was related to a younger age ($p < 0.001$), black race ($p = 0.005$), a higher BMI ($p < 0.001$), and recruitment in 2005–2009 ($p = 0.03$). PSA at diagnosis was not associated with BMI or physical activity ($p \geq 0.14$, Supplementary Table 1).

First, we evaluated whether BMI and physical activity were associated with tumor characteristics at the time of surgery (Table 3, Supplementary Tables 2 and 3). In univariate analyses, patients who had a higher BMI had a higher prostate weight [odds ratios (OR) 1.13, $p = 0.03$], and a similar trend was noted in physically active patients (OR 1.31, $p = 0.07$). Patients with a higher BMI also had more frequently high-risk PCa (OR 1.21, $p = 0.002$) and a higher

Table 1 Baseline characteristics of our cohort of radical prostatectomy patients in Quebec, grouped by BMI

	Normal weight (BMI 18.5–24.9)	Overweight (BMI 25.0–29.9)	Obesity		*p* value[a]
			Class 1 (BMI 30.0–34.9)	Class 2/3 (BMI ≥ 35)	
# of patients	508	877	274	55	
Age at radical prostatectomy					
Median (95% CI)	62 (62–63)	63 (63–64)	62 (61–62)	61 (58–62)	
41–50	22 (4.3%)	31 (3.5%)	17 (6.2%)	3 (5.5%)	**0.02**
51–60	173 (34.1%)	286 (32.6%)	103 (37.6%)	24 (43.6%)	
61–70	264 (52.0%)	493 (56.2%)	144 (52.6%)	27 (49.1%)	
71–80	49 (9.6%)	67 (7.6%)	10 (3.6%)	1 (1.8%)	
Race					
White	448 (88.2%)	773 (88.1%)	245 (89.4%)	42 (90.9%)	
Nonwhite	24 (4.7%)	43 (4.9%)	11 (4.0%)	2 (3.6%)	0.91
Asian	16 (3.1%)	7 (0.8%)	2 (0.7%)	0 (0.0%)	**0.003**
Black	6 (1.2%)	24 (2.7%)	8 (2.9%)	2 (3.6%)	0.25
American native	2 (0.4%)	12 (1.4%)	1 (0.4%)	0 (0.0%)	0.17
Mixed race	8 (1.6%)	14 (1.6%)	3 (1.1%)	1 (1.8%)	0.94
Not answered	28 (5.5%)	47 (5.4%)	15 (5.5%)	2 (3.6%)	
Family history of prostate cancer					
No	262 (51.6%)	425 (48.5%)	136 (49.6%)	28 (50.9%)	0.57
Yes	177 (34.8%)	333 (38.0%)	112 (40.9%)	21 (38.2%)	
Not answered	69 (13.6%)	119 (13.6%)	26 (9.5%)	6 (10.9%)	
Physical activity in past 12 months					
None	10 (2.0%)	33 (3.8%)	11 (4.0%)	2 (3.6%)	**< 0.001**
< 1 h/week	25 (4.9%)	74 (8.4%)	32 (11.7%)	7 (12.7%)	
1–4 h/week	227 (44.7%)	399 (45.5%)	127 (46.4%)	29 (52.7%)	
> 4 h/week	220 (43.3%)	312 (35.6%)	73 (26.6%)	8 (14.5%)	
Not answered	26 (5.1%)	59 (6.7%)	31 (11.3%)	9 (16.4%)	
PSA at diagnosis					
Median (95% CI)	5.9 (5.7–6.2)	5.9 (5.7–6.1)	5.6 (5.2–6.2)	6.4 (5.3–7.1)	
< 5.00 ng/ml	167 (32.9%)	305 (34.8%)	106 (38.7%)	19 (34.5%)	0.38
5.00–7.49 ng/ml	172 (33.9%)	289 (33.0%)	72 (26.3%)	19 (34.5%)	
≥ 7.50 ng/ml	168 (33.1%)	274 (31.2%)	93 (33.9%)	15 (27.3%)	
Not answered	1 (0.2%)	9 (1.0%)	3 (1.1%)	2 (3.6%)	
Hospital of surgery					
Hospital 1	151 (29.7%)	194 (22.1%)	85 (31.0%)	15 (27.3%)	0.07
Hospital 2	118 (23.2%)	236 (26.9%)	68 (24.8%)	12 (21.8%)	
Hospital 3	138 (27.2%)	245 (27.9%)	85 (23.7%)	15 (27.3%)	
Hospital 4	101 (19.9%)	202 (23.0%)	56 (20.4%)	13 (23.6%)	
Year of surgery					
Median (95% CI)	2010 (2009–2010)	2010 (2010)	2010 (2009–2010)	2009 (2008–2010)	
2005–2009	251 (49.4%)	393 (44.8%)	136 (49.6%)	31 (56.4%)	0.14
2010–2014	257 (50.6%)	484 (55.2%)	138 (50.4%)	24 (43.6%)	

[a]Chi^2 tests were conducted to calculate *p* values

CAPRA-S score (OR 1.22, $p = 0.02$), as they had more T3 tumors (OR 1.16, $p = 0.01$).

In multivariate analyses, adjusting for age, race, hospital of surgery and physical activity, a higher BMI remained associated with increased prostate weight (OR 1.16, $p = 0.02$), T3 tumors (OR 1.19, $p = 0.01$), higher Gleason at surgery (OR 1.15, $p = 0.03$), high-risk PCa (OR 1.27, $p = 0.001$), and a higher CAPRA-S score (OR 1.23, $p = 0.04$). However, no clear correlation was found between physical activity and surgery outcomes; while medium physical activity decreased the risk for T3 tumors (OR 0.67, $p = 0.02$) and high-risk PCa (OR 0.69, $p = 0.03$), patients with high physical activity did

Table 2 Baseline characteristics of our cohort of radical prostatectomy patients in Quebec, grouped by average weekly physical activity in the year prior to radical prostatectomy

	Low < 1 h/week	Medium 1–4 h/week	High > 4 h/week	*p* value[a]
# of patients	201	817	633	
Age at radical prostatectomy				
Median (95% CI)	60 (59–61)	63 (62–63)	64 (63–64)	
41–50	11 (5.5%)	41 (5.0%)	24 (3.8%)	**< 0.001**
51–60	99 (49.3%)	282 (34.5%)	176 (27.8%)	
61–70	86 (42.8%)	436 (53.4%)	375 (59.2%)	
71–80	4 (2.8%)	58 (7.1%)	58 (9.2%)	
Race				
White	171 (85.1%)	711 (87.0%)	570 (90.0%)	
Nonwhite	18 (9.5%)	40 (4.9%)	25 (3.9%)	**0.02**
Asian	4 (2.0%)	9 (1.1%)	10 (1.6%)	0.56
Black	10 (5.0%)	25 (3.1%)	8 (1.3%)	**0.01**
American native	4 (2.0%)	6 (0.7%)	7 (1.1%)	0.27
Mixed race	4 (2.0%)	12 (1.5%)	9 (1.4%)	0.80
Not answered	8 (4.0%)	54 (6.6%)	29 (4.6%)	
Family history of prostate cancer				
No	95 (47.3%)	406 (49.7%)	310 (49.0%)	0.99
Yes	72 (35.8%)	316 (38.7%)	240 (37.9%)	
Not answered	34 (16.9%)	95 (11.6%)	83 (13.1%)	
BMI				
18.5–24.9 (normal weight)	35 (17.4%)	227 (27.8%)	220 (34.8%)	**< 0.001**
25.0–29.9 (overweight)	107 (53.2%)	399 (48.8%)	312 (49.3%)	
30.0–34.9 (obesity class 1)	43 (21.4%)	127 (15.5%)	73 (11.5%)	
≥ 35.0 (obesity class 2–3)	9 (4.5%)	29 (3.5%)	8 (1.3%)	
Not answered	7 (3.5%)	35 (4.3%)	20 (3.2%)	
PSA at diagnosis				
Median (95% CI)	5.9 (5.4–6.4)	5.9 (5.7–6.1)	5.9 (5.6–6.1)	
< 5.00 ng/ml	68 (33.8%)	290 (35.5%)	218 (34.4%)	0.98
5.00–7.49 ng/ml	66 (32.8%)	265 (32.4%)	212 (33.5%)	
≥ 7.50 ng/ml	65 (32.3%)	254 (31.1%)	197 (31.1%)	
Not answered	2 (1.0%)	8 (1.0%)	6 (0.9%)	
Hospital of surgery				
Hospital 1	57 (28.4%)	229 (28.0%)	148 (23.4%)	**0.01**
Hospital 2	55 (27.4%)	208 (25.5%)	154 (24.3%)	
Hospital 3	49 (24.4%)	209 (25.6%)	182 (28.8%)	
Hospital 4	40 (19.9%)	171 (20.9%)	149 (23.5%)	
Year of surgery				
Median (95% CI)	2010 (2009–2010)	2010 (2009–2010)	2010 (2010)	
2005–2009	100 (49.8%)	391 (47.9%)	264 (41.7%)	**0.03**
2010–2014	101 (50.2%)	426 (52.1%)	369 (58.3%)	

[a]Chi^2 tests were conducted to calculate *p* values

not have such decreased risks ($p \geq 0.10$). The odds for positive surgical margins were increased when a patient had a higher BMI or high physical activity levels, but this was not significant (OR 1.13 and 1.24, respectively; $p \geq 0.08$). Results were similar when adding the variables PSA before surgery, a positive PCa family history, and year of surgery to the multivariate model too (Table 3).

Next, we evaluated whether BMI and physical activity were predictive for time to treatment failure after surgery. While the treatment failure curve for obese patients seemed slightly steeper, treatment failure rates did not differ significantly between the four BMI groups ($p = 0.516$, Fig. 2a). A direct comparison between all patients that had a normal weight to all obese patients did not reveal significant

Table 3 Univariate and multivariate (ordered) logistic regressions to evaluate associations between BMI, physical activity, and surgery outcome

Dependent variable (outcome)	Independent variable (exposure)	Univariate analysis		Multivariate analysis[j]		Multivariate analysis[k]	
		Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Prostate weight[c]	BMI[a]	**1.13 (1.02–1.26)**	**0.03**	**1.16 (1.03–1.32)**	**0.02**	1.11 (0.98–1.27)	0.10
TNM-T stage[d]		**1.16 (1.04–1.30)**	**0.01**	**1.19 (1.04–1.36)**	**0.01**	**1.22 (1.06–1.41)**	**0.005**
TNM-N stage[e]		1.20 (0.90–1.61)	0.22	1.20 (0.86–1.66)	0.28	1.29 (0.90–1.87)	0.17
Gleason at surgery[f]		1.21 (0.97–1.09)	0.14	**1.15 (1.02–1.31)**	**0.03**	1.13 (0.98–1.29)	0.19
Positive surgical margins[g]		1.12 (0.99–1.27)	0.07	1.13 (0.99–1.30)	0.08	1.14 (0.98–1.32)	0.09
Advanced prostate cancer[h]		**1.21 (1.07–1.36)**	**0.002**	**1.27 (1.10–1.46)**	**0.001**	**1.33 (1.14–1.55)**	**< 0.001**
CAPRA-S score[i]		**1.22 (1.03–1.45)**	**0.02**	**1.23 (1.01–1.51)**	**0.04**	**1.27 (1.02–1.59)**	**0.04**
Prostate weight[c]	Average weekly physical activity[b]						
	Low	1.0 (ref.)					
	Medium	1.22 (0.91–1.63)	0.18	1.23 (0.91–1.67)	0.18	1.28 (0.92–1.78)	0.14
	High	1.31 (0.98–1.76)	0.07	1.19 (0.86–1.63)	0.29	1.23 (0.87–1.73)	0.24
TNM-T stage[d]	Low	1.0 (ref.)					
	Medium	0.79 (0.58–1.07)	0.13	**0.67 (0.48–0.93)**	**0.02**	**0.67 (0.47–0.96)**	**0.03**
	High	0.86 (0.62–1.17)	0.33	0.75 (0.54–1.06)	0.10	0.78 (0.54–1.13)	0.13
TNM-N stage[e]	Low	1.0 (ref.)					
	Medium	1.13 (0.51–2.51)	0.77	1.14 (0.50–2.59)	0.75	1.66 (0.57–4.87)	0.35
	High	1.07 (0.47–2.43)	0.86	1.20 (0.51–2.79)	0.68	1.96 (0.65–5.89)	0.23
Gleason at surgery[f]	Low	1.0 (ref.)					
	Medium	1.07 (0.80–1.42)	0.66	0.97 (0.72–1.31)	0.83	1.08 (0.77–1.51)	0.65
	High	1.13 (0.84–1.51)	0.43	1.02 (0.74–1.40)	0.90	1.12 (0.79–1.58)	0.54
Positive surgical margins[g]	Low	1.0 (ref.)					
	Medium	1.17 (0.84–1.63)	0.37	1.06 (0.75–1.50)	0.76	1.09 (0.74–1.60)	0.68
	High	1.32 (0.94–1.85)	0.11	1.24 (0.86–1.77)	0.25	1.22 (0.82–1.81)	0.33
Advanced prostate cancer[h]	Low	1.0 (ref.)					
	Medium	0.80 (0.58–1.09)	0.15	**0.69 (0.50–0.97)**	**0.03**	0.69 (0.47–1.01)	0.06
	High	0.91 (0.66–1.26)	0.57	0.83 (0.59–1.17)	0.29	0.84 (0.57–1.25)	0.39
CAPRA-S score[i]	Low	1.0 (ref.)					
	Medium	1.24 (0.80–1.91)	0.34	1.17 (0.74–1.85)	0.49	1.03 (0.60–1.76)	0.92
	High	1.01 (0.65–1.57)	0.95	1.04 (0.65–1.66)	0.87	0.96 (0.56–1.67)	0.89

[a]Patients were not stratified based on BMI; BMI was used as a continuous variable. Odds ratios were calculated per 5 kg/m^2 increase

[b]Patients were divided into three groups based on their average physical activity in the past 12 months [< 1 h/week (low), 1–4 h/week (medium), and > 4 h/week (high)]

[c]Prostate weight was divided into four groups (approximate quartiles): ≤ 35.0, 35.0–50.0, 50.0–70.0 g, or > 70.0 g

[d]Pathological T stage was divided into three groups: pT2, pT3a, or pT3b

[e]Pathological N stage was divided into pN0 or pN1

[f]Gleason scores were grouped using the ISUP 2014 5-tier grade groups: group 1 (Gleason 6), group 2 (Gleason 3 + 4), group 3 (Gleason 4 + 3), group 4 (Gleason 8), and group 5 (Gleason 9–10)

[g]Positive surgical margins were a dichotomous variable (yes/no)

[h]Advanced prostate cancer is defined as pathologic T3, pathologic N1, and/or Gleason 8–10

[i]The CAPRA-S score was grouped by 0–2, 3–5, and 6 and above

[j]Adjusted for age, race, hospital of surgery, and physical activity (top) or BMI (bottom)

[k]Adjusted for age, race, hospital of surgery, physical activity (top) or BMI (bottom), PSA before surgery, a positive family history, and year of surgery

differences between the two groups either ($p = 0.197$, Supplementary Figure 1). Importantly, the hazard ratio for treatment failure was independent of BMI (hazard ratio 0.95, $p = 0.54$) when adjusting for tumor characteristics that are known to predict treatment failure, such as Gleason score (Table 4). No differences were observed in treatment failure rates between patients based on their physical activity ($p = 0.797$, Fig. 2b). Uni- and multivariate Cox

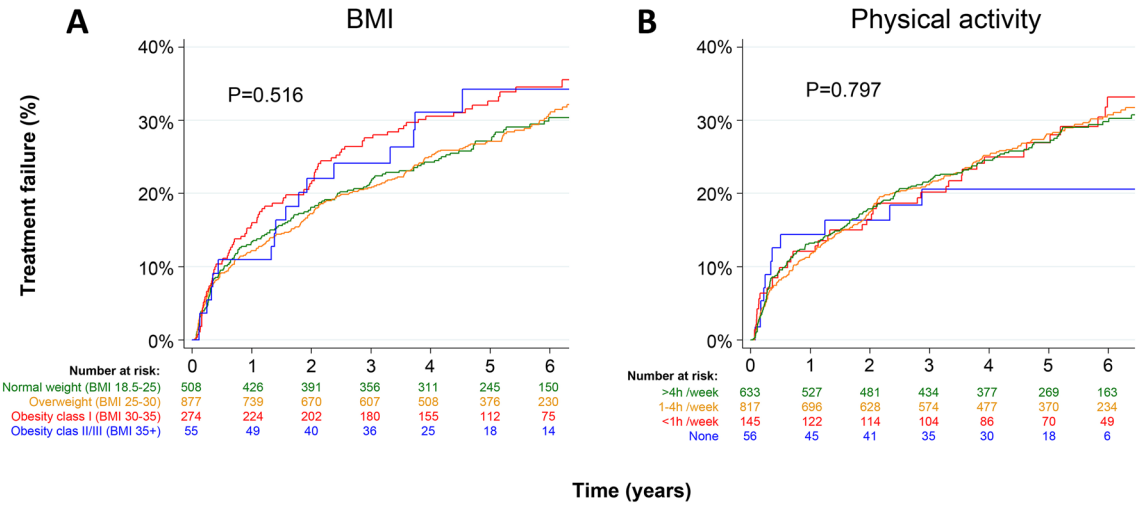

Fig. 2 Treatment failure after radical prostatectomy for localized prostate cancer. Patients were stratified by body-mass index (BMI) (**a**) or average weekly physical activity in the year prior to radical prostatectomy (**b**)

Table 4 Univariate and multivariate treatment failure analyses using the Cox proportional-hazards model

Variable	Univariate analysis		Multivariate analysis[c]		Multivariate analysis[d]	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
BMI[a]	1.03 (0.93–1.15)	0.53	1.03 (0.91–1.16)	0.66	0.95 (0.79–1.13)	0.54
Average weekly physical activity[b]						
Low	1.0 (ref.)					
Medium	1.05 (0.78–1.41)	0.74	1.00 (0.74–1.36)	0.99	0.82 (0.55–1.23)	0.34
High	1.00 (0.73–1.35)	0.98	0.98 (0.71–1.35)	0.90	0.85 (0.56–1.29)	0.45

[a]Patients were not stratified based on BMI; BMI was used as a continuous variable. Odds ratios were calculated per 5 kg/m^2 increase

[b]Patients were divided into three groups based on their average physical activity in the past 12 months [< 1 h/week (low), 1–4 h/week (medium), > 4 h/week (high)]

[c]Adjusted for age, race, hospital of surgery, and physical activity (top row) or BMI (bottom row)

[d]Adjusted for age, race, hospital of surgery, CAPRA-S score, and physical activity (top row), or BMI (bottom row)

proportional-hazards models confirmed this lack of association (hazard ratio 1.00 and 0.85, $p > 0.4$; Table 4).

Discussion

Evaluating data from PCa patients included in the prospective PROCURE biobank and cohort study, BMI, but not physical activity, was related to locally advanced and high-risk PCa, while neither variable correlated with treatment failure after surgery.

Previously, meta-analyses reported that PCa incidence was significantly increased in obese men and that obese men presented with more advanced and fatal PCa [5–7, 19]. These associations differed between geographic regions: the association was found in European and Australian studies, but generally not in American studies. It was hypothesized that this difference was caused by higher PSA screening rates in North America. However, locally advanced and higher risk disease was also associated with a higher BMI in our Canadian cohort, while PSA screening rates in the US and Canada are relatively similar [20, 21]. Other parameters such as socioeconomic status may explain geographical differences in association between BMI and PCa. Our findings correspond to the proposed hypothesis that detection of PCa may be delayed in obese patients, resulting in more advanced and higher risk disease at the time of diagnosis [5, 22]. BMI was not only associated with higher risk and advanced disease, but also with increased prostate weight in our cohort. Furthermore, despite the larger prostate, BMI did not predict PSA levels, which might indicate hemodilution.

If obese PCa patients have a worse outcome, it suggests that weight control may effectively improve morbidity and mortality [23]. Currently, studies are ongoing that evaluate

the effect of weight loss on PCa outcome [24]. However, no meta-analysis has been able to rule out publication bias, and recently published, large cohort studies did not find an association between BMI and recurrence of PCa after surgery either [6–9]. Our cohort is larger than most aforementioned studies and confirms this lack of association between BMI and clinical outcome. Future studies are needed to assess whether subgroups of obese PCa patients may have a worse prognosis, such as patients having central adiposity, and whether the development of castration resistance is related to BMI. Furthermore, considering that most PCa patients die from non-cancerous, lifestyle-related causes, weight control should be encouraged in PCa patients to decrease obesity-related disease, similar to the general population [2].

An association between physical activity and PCa is even more disputed. A systematic review reported an association between PCa incidence and total and occupational physical activity, but not recreational physical activity [25]. This association was only found in studies from Europe and the United States, but not in Canadian or Asian studies. Furthermore, many studies assessing physical activity and PCa did not adjust for BMI, while these parameters are strongly correlated. A weak association has been reported between physical activity and advanced PCa or PCa mortality [26, 27]. However, in line with other large cohort studies, we do not find an association between physical activity and locally advanced, high-risk PCa, or treatment failure [13].

The advantages of our study are that the patients represent an average Canadian population of men with localized PCa undergoing radical prostatectomy, as we minimized exclusion criteria and included the four major centers in Quebec performing radical prostatectomies. The similarity to a general population was confirmed by the similar weight distribution in our cohort compared to the general Quebec population [28]. Furthermore, our study contained one of the largest PCa populations in which BMI and physical activity are both studied as potential determinants for advanced and/or aggressive PCa, and contains, to our knowledge, the largest surgically treated PCa patient population after 2000 in which the role of BMI and physical activity is studied together. Considering that BMI and physical activity are closely related to each other, we find it important that studies evaluate both. Finally, surgery specimens were histologically evaluated using a standardized protocol by specialized genitourinary pathologists using the 2014 ISUP guidelines.

Seemingly contradictory to the existing literature, older patients in our cohort had a lower BMI and were physically more active, while usually older patients have a higher weight and are less active. Most likely, this difference occurred due to selection bias for patients undergoing radical prostatectomy. A good physical condition will be necessary for this population when undergoing major surgery, making obese and/or physically inactive patients less suitable candidates. Hence, only the fittest older patients were selected for radical prostatectomy.

The primary limitation in our data is that both BMI and physical activity were self-reported. Men are known to generally underreport weight [29, 30]. Waist circumference was not measured. Recall bias may have occurred. Misclassification in physical activity reporting may have occurred as well, particularly as PROCURE did not use standardized tests such as the International Physical Activity Questionnaire, and as we grouped all types of physical activity (moderate and vigorous). We improved the accuracy of our reporting by comparing answers to various questions to assess weight (current weight, weight at the age of 30, weight loss, etc.) and physical activity (physical activity in the past 12 months and current physical activity); patients were excluded if large, unexplained differences existed. Importantly, a direct comparison of patients with a normal weight (BMI 18.5–25) to obese patients (BMI 30 +), and the least active to the most active patient group (< 1 h/week and > 4 h/week) provided similar results as presented (Supplementary Table 4, Supplementary Figure 1), while it is highly unlikely that the average BMI and physical activity were similar between these groups due to gross misclassification. Other limitations include potential residual confounding and that the database is not mature enough yet for evaluation of other outcomes, such as castration resistance and mortality.

Conclusions

This large, prospective cohort study in Quebec, Canada, suggests that obese PCa patients present more often with locally advanced, high-risk disease at the time of radical prostatectomy. However, BMI and physical activity did not predict independently the time to treatment failure after surgery, suggesting that these parameters should not impact follow-up decisions.

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Author contributions MW: project development, data management, data analyses, and manuscript writing. SC: project development, data collection and management, and manuscript editing. GM: data collection and management and manuscript editing. CL: data analyses and manuscript editing. SA: data collection and management and manuscript editing. AO: data collection and management and manuscript editing. ES: data collection and manuscript editing. FS: project

development, data collection, and manuscript editing. MC: project development, data collection, and manuscript editing. LL: project development, data collection, and manuscript editing. FB: data collection and manuscript editing. ML: data collection and manuscript editing. NE: data collection and manuscript editing. BT: data collection and manuscript editing. AA: principal investigator, project development, data analyses, and manuscript writing.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Siegel RL, Miller KD (2018) Jemal A (2018) Cancer statistics. CA Cancer J Clin 68(1):7–30. https://doi.org/10.3322/caac.21442
2. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO (2012) Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 104(17):1335–1342. https://doi.org/10.1093/jnci/djs299
3. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA (2016) The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 40(2):244–252. https://doi.org/10.1097/pas.0000000000000530
4. International Agency for Research on Cancer (World Health Organization). List of classifications by cancer sites with sufficient or limited evidence in humans, vol 1–121. https://monographs.iarc.fr/wp-content/uploads/2018/06/Table4.pdf. Accessed 21 Aug 2018
5. Allott EH, Masko EM, Freedland SJ (2013) Obesity and prostate cancer: weighing the evidence. Eur Urol 63(5):800–809. https://doi.org/10.1016/j.eururo.2012.11.013
6. Cao Y, Ma J (2011) Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Philadelphia, Pa) 4(4):486–501. https://doi.org/10.1158/1940-6207.capr-10-0229
7. Hu MB, Xu H, Bai PD, Jiang HW, Ding Q (2014) Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Med Oncol (Northwood, London, England) 31(2):829. https://doi.org/10.1007/s12032-013-0829-8
8. Kok DE, van Roermund JG, Aben KK, van de Luijtgaarden MW, Karthaus HF, van Vierssen Trip OB, Kampman E, Alfred Witjes J, Kiemeney LA (2011) Body mass index is not a predictor of biochemical recurrence after radical prostatectomy in Dutch men diagnosed with prostate cancer. World J Urol 29(5):695–701. https://doi.org/10.1007/s00345-010-0629-0
9. Narita S, Mitsuzuka K, Yoneyama T, Tsuchiya N, Koie T, Kakoi N, Kawamura S, Kaiho Y, Ohyama C, Tochigi T, Yamaguchi T, Habuchi T, Arai Y (2013) Impact of body mass index on clinicopathological outcome and biochemical recurrence after radical prostatectomy. Prostate Cancer Prostat Dis 16(3):271–276. https://doi.org/10.1038/pcan.2013.16
10. Cuzick J, Thorat MA, Andriole G, Brawley OW, Brown PH, Culig Z, Eeles RA, Ford LG, Hamdy FC, Holmberg L, Ilic D, Key TJ, La Vecchia C, Lilja H, Marberger M, Meyskens FL, Minasian LM, Parker C, Parnes HL, Perner S, Rittenhouse H, Schalken J, Schmid HP, Schmitz-Drager BJ, Schroder FH, Stenzl A, Tombal B, Wilt TJ, Wolk A (2014) Prevention and early detection of prostate cancer. Lancet Oncol 15(11):e484–e492. https://doi.org/10.1016/s1470-2045(14)70211-6
11. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM (2011) Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol 29(6):726–732. https://doi.org/10.1200/jco.2010.31.5226
12. Wekesa A, Harrison M, Watson RW (2015) Physical activity and its mechanistic effects on prostate cancer. Prostate Cancer Prostat Dis 18(3):197–207. https://doi.org/10.1038/pcan.2015.9
13. Moore SC, Peters TM, Ahn J, Park Y, Schatzkin A, Albanes D, Ballard-Barbash R, Hollenbeck A, Leitzmann MF (2008) Physical activity in relation to total, advanced, and fatal prostate cancer. Cancer Epidemiol Biomark Prev 17(9):2458–2466. https://doi.org/10.1158/1055-9965.epi-08-0403
14. Wiklund F, Lageros YT, Chang E, Balter K, Johansson JE, Adami HO, Gronberg H (2008) Lifetime total physical activity and prostate cancer risk: a population-based case-control study in Sweden. Eur J Epidemiol 23(11):739–746. https://doi.org/10.1007/s10654-008-9294-7
15. Defining Adult Overweight and Obesity, Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion Centers for Disease Control and Prevention. https://www.cdc.gov/obesity/adult/defining.html. Last updated: 16 Jun 2016; Last accessed: 12 Jul 2017
16. United States Food and Drug Administration [2016], Collection of Race and Ethnicity Data in Clinical Trials, Guidance for Industry and Food and Drug Administration Staff. https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf. Last accessed: 12 Jul 2017
17. Cooperberg MR, Hilton JF, Carroll PR (2011) The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 117(22):5039–5046. https://doi.org/10.1002/cncr.26169
18. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53(282):457–481
19. Discacciati A, Orsini N, Wolk A (2012) Body mass index and incidence of localized and advanced prostate cancer–a dose-response meta-analysis of prospective studies. Ann Oncol 23(7):1665–1671. https://doi.org/10.1093/annonc/mdr603
20. Jemal A, Fedewa SA, Ma J, Siegel R, Lin CC, Brawley O, Ward EM (2015) Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA J Am Med Assoc 314(19):2054–2061. https://doi.org/10.1001/jama.2015.14905
21. Canadian Community Health Survey (2014) Statistics Canada, public use microdata file, statistics Canada. http://dli-idd-nesstar.statcan.gc.ca/webview/index.jsp?object=http://dli-idd-nesstar.statcan.gc.ca:80/obj/fCatalog/Catalog85. Accessed 21 Aug 2018
22. Freedland SJ, Platz EA, Presti JC Jr, Aronson WJ, Amling CL, Kane CJ, Terris MK (2006) Obesity, serum prostate specific

antigen and prostate size: implications for prostate cancer detection. J Urol 175(2):500–504. https://doi.org/10.1016/s0022-5347(05)00162-x **(discussion 504)**

23. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, Freedland SJ, Walsh PC, Platz EA (2011) Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev Res (Philadelphia, Pa) 4(4):544–551. https://doi.org/10.1158/1940-6207.capr-10-0257
24. United States National Library of Medicine (National Institutes of Health) [2017], Weight Management Aimed to Reduce Risk and Improve Outcomes From Radical Prostatectomy (WARRIOR). https://clinicaltrials.gov/ct2/show/NCT03261271. Last accessed: 4 Dec 2017
25. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R, Zhao Y (2011) Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. Eur Urol 60(5):1029–1044. https://doi.org/10.1016/j.eururo.2011.07.007
26. Hrafnkelsdottir SM, Torfadottir JE, Aspelund T, Magnusson KT, Tryggvadottir L, Gudnason V, Mucci LA, Stampfer M, Valdimarsdottir UA (2015) Physical activity from early adulthood and risk of prostate cancer: a 24-year follow-up study among Icelandic men. Cancer Prev Res (Philadelphia, Pa) 8(10):905–911. https://doi.org/10.1158/1940-6207.capr-15-0035
27. Nilsen TI, Romundstad PR, Vatten LJ (2006) Recreational physical activity and risk of prostate cancer: a prospective population-based study in Norway (the HUNT study). Int J Cancer 119(12):2943–2947. https://doi.org/10.1002/ijc.22184
28. Navaneelan T, Janz T (2014) Adjusting the scales: Obesity in the Canadian population after correcting for respondent bias. Statistics Canada, Catalogue no 82-624-X:1-10
29. Richmond TK, Walls CE, Austin SB (2012) Sexual orientation and bias in self-reported BMI. Obesity (Silver Spring, Md) 20(8):1703–1709. https://doi.org/10.1038/oby.2012.9
30. Scribani M, Shelton J, Chapel D, Krupa N, Wyckoff L, Jenkins P (2014) Comparison of bias resulting from two methods of self-reporting height and weight: a validation study. JRSM Open 5(6):2042533313514048. https://doi.org/10.1177/2042533313514048